REMARKS

Claims 1-60 are pending in the present application and subject to restriction a restriction requirement under 35 U.S.C. § 121. Claims 1-60 are rejected under 35 USC § 101; provisionally rejected under the judicially created doctrine of obviousness-type double patenting; rejected under 35 USC § 112, first paragraph; and rejected under 35 USC § 103. Applicants respectfully traverse these rejections and request withdrawal of these rejections based on the following remarks.

I. Applicants' Invention.

Applicants' invention is directed to substituted diaryl sulfide cinnamide compounds as described on page 4, lines 12-20, of the specification. Each of the claims requires a diaryl sulfide compound that is either *ortho-* (*i.e.*, the R_1 position), or *para-* (*i.e.*, the R_3 position) substituted with a "cinnamide" group. Over 400 examples of compounds within the description of the present invention have been prepared. Each of these examples is either an *ortho-* substituted "cinnamide" aryl-phenylsulfide compound, or a *para-* substituted "cinnamide" aryl-phenylsulfide compound.

The compounds of Applicants invention have a common utility. This common utility is described on page 4 of the specification. In particular, the diaryl sulfide cinnamide compounds of Applicants' invention bind to the interaction-domain (I-domain) of LFA-1. Binding to the I-domain of LFA-1 interrupts endothelial cell-leukocyte adhesion by blocking the interaction of LFA-1 with the ICAMs, thus suppressing an inflammatory response. Compounds that block the LFA-1/ICAM interaction and suppress inflammatory responses are useful for treating inflammatory and immune diseases such as, arthritis, asthma, inflammatory lung injury, inflammatory bowel disease, autoimmune diseases, tumor metastasis, allograft rejection and reperfusion injury. (Specification, pages 412-416).

II. Response to Election/Restriction Requirement

Claims 1-60 are pending in the application and subject to a restriction requirement under 35 U.S.C. § 121 as stated on pages 8-10 of the Office Action dated February 27, 2002 in numbered paragraphs I-VI. Applicants respectfully traverse the present restriction requirement as improper under US Patent Office practice and procedure for the restriction of a Markush-type claim. Applicants request reconsideration and withdrawal of the restriction requirement based on the following remarks.

The undersigned, as Applicant's representative, would again like to thank Examiner Patel for the telephone interview on May 2, 2002 regarding the Restriction/Election requirement in Applicants co-pending case, Application Serial No. 09/695,040. If, notwithstanding Applicants' present request for reconsideration, the Examiner maintains that an Election/Restriction Requirement of some nature should be made, Applicants propose that the claims be divided into alternate restriction Groups A-C as detailed below. These alternate Restriction Groups were suggested and preliminarily agreed upon with the Examiner in the May 2, 2002 telephone interview for Application Serial No. 09/695,040 and are presented again in this Application for consideration by the Examiner.

A. Restriction Is Improper Because There is Unity Of Invention.

Under MPEP § 803.02, restriction of a Markush-type claim is improper, even where the claims are directed to what would otherwise be considered independent and distinct inventions, if the subject matter of the claim has unity of invention. The presently proposed restriction requirement does not fall within the US Patent Office guidelines because the compounds of the present invention, included in the Markush groups in claims 1 and 47, do in fact have clear unity of invention. In particular, the compounds: (1) share a common utility (*i.e.*, they are LFA-1 antagonists); and (2) share a structural feature essential to that utility (*i.e.*, they are all diaryl sulfide cinnamide compounds and the linking sulfide is required for that utility).

1. The PTO Acknowledges that there is Common Utility

The Office states that "[c]ompounds having the structures identified in the claim(s) while possessing a single common utility, ..."), thus admitting that the first USPTO requirement for a proper Markush group, *i.e.*, common utility is satisfied. *See*, Office Action dated February 27, 2002, page 3, lines 10-11.

2. There Are Common Structural Features Essential to the Asserted Utility

In the present Office Action, the Office incorrectly states that the compounds having the structures identified in the claims "do not represent the same structure because in addition to variations of Formulae as recited by Formula I, II, III . . . ." In response, Applicants would like to point out that Formulas I and III have the same generic structure, with substituent definitions (*e.g.*, R1-R5) that vary in scope. All claims containing generic Formulas I or III contain the proviso that there is either *ortho-* or *para-* "cinnamide" substitution on the phenyl ring (*e.g.*, R1 or R3 is a "cinnamide"). The common generic structural feature of Formulas I and III, include (i) a linking "sulfide" moiety; (ii) a phenyl ring; and (iii) a "cinnamide" group placed *ortho-* or *para-* to the linking "sulfide." These common structural features allow the Examiner to appropriately classify and search the compounds of Formulas I and III together.

Applicants' compounds, as claimed in Formulas I and III, have a common structural feature essential to the asserted utility. The present invention discloses a series of LFA-1 diaryl sulfide "cinnamide" antagonists that were developed by transforming an anilino-based diaryl sulfide into the cinnamide-based diaryl sulfides through identification of an additional binding pocket. *See*, Liu, G., *et al.*, *J. Med. Chem,*. (2000), 43, 4025-4040; Liu, G., *Expert Opin. Ther. Patents* (2001) 11(9):1383-1393, submitted herewith in an accompanying IDS (filed on July 29, 2002 by US Mail).

In the *Expert Opin. Ther. Patents* article to Liu, G., a number of diaryl sulfide species, including an earlier discovered diaryl sulfide anilino compound, are identified. This article

specifies that the sulfide group is required for the affinity that results in the utility of the compounds as LFA-1 antagonists. In reference to the anilino compound, the article states "[i]nitial SAR indicates that both the sulfide and the anilino group are required for affinity." *Id.* at 1387 (emphasis added). The *J. Med. Chem.* article to Liu, G., *et al.*, describes the discovery of *ortho*- and *para*- ethenylcarbonyl linkers (*i.e.*, a "cinnamide" substituent). The compounds of the present invention all possess the sulfide and ethenylcarbonyl linkers, identified in the Liu articles as optimal for accessing the binding pocket, which regulates the interaction between LFA-1 and its natural ligands.

In response to the assertion of the Office that "[t]he variations of Ar, R10/R11 in Formula if claim 1 produce different entities that is [sic] presently multiple search areas" (Office Action, page 4, lines 10-11), Applicants agree that Examination of the claimed invention may involve searching in multiple subclasses. However, given the nature of Applicants' invention, (*e.g.*, individual compounds each with Ar and NR_{10} R_{11} in different subclasses), it is believed that there is no proper or meaningful way to group the invention that does not involve searching in multiple subclasses. Whether a Markush group has substituents involved in multiple subclasses is not the test for an appropriate restriction requirement. Provided that the Markush group has "common utility" and a "common structural feature," essential to that utility, as is the case here, the Markush group is proper under the Patent Office guidelines. MPEP § 803.02. Accordingly, Applicants request withdrawal of the Election/Restriction requirement.

B. The Present Groupings Unreasonably Restrict Applicants' Available Patent Rights in Their Invention.

In the present Office Action, dated February 27, 2002, the Examiner identifies six different groups of compounds that restrict Applicants' invention as provided in numbered paragraphs I-VI thereof. This restriction improperly dismembers Applicants' invention into groups that diminish the total patent rights that are otherwise statutorily available to the Applicants. In *In re Weber*, 198 U.S.P.Q. 328, 331 (C.C.P.A. 1978), the court determined

that 35 USC § 112, second paragraph, allows an inventor to claim the invention as he contemplates it. Furthermore, when weighing the effect of "such administrative matters as examiner case loads and the amount of searching done per filing fee" versus Applicants' statutory rights, the *Weber* court stated "[w]e conclude that the statutory rights [of the applicant] is paramount." *Id.* at 332. Under the present restriction requirement, even if separate divisional applications were filed, corresponding to each of the six groups proposed by the PTO, Applicants could never effectively claim the full scope of their disclosed invention.

The species that Applicants seek to have examined is [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl) phenyl]sulfide (Compound 423B). The Examiner incorrectly states on page 12 of the present Office Action that Compound 423B falls into Group II. For Compound 423B, Ar = **a substituted aryl group**, substituted with a substituted heterocycle. The Ar substituent in Compound 423B does not fall within Group II in which Ar = 6 membered heterocycles having only 1 N.

Compound 423B, and any other compound in which Ar = aryl and R_{10} and R_{11} are taken together with N to form a heterocyclyl group, do not fall within any Group that encompasses Formula I (*i.e.*, Groups I-III). Many of the Applicants' disclosed species have Ar and $NR_{10}R_{11}$ substituents that are in different subclasses. Restriction groups simply cannot be formed in which Ar and $NR_{10}R_{11}$ substituents are represented in the same subclass and still allow the Applicants to claim their statutorily entitled invention.

Group V, which includes Compound 423B, is arbitrarily restricted to Claims 27-60 and Formula III. There is no Group that includes Compound 423B and Claim 1, Formula I. Applicants are statutorily entitled to Examination of all of their invention. This includes Claim 1, Formula I, and all of Applicants disclosed species. The present restriction requirement does accomplish this. Accordingly, Applicants request withdrawal of the present restriction requirement on this basis.

C. Proposed Election/Restriction Requirement

If, notwithstanding Applicants' present request for reconsideration, the Examiner maintains that an Election/Restriction Requirement of some nature should be made, Applicants propose that the claims be divided into the following Groups A-C.

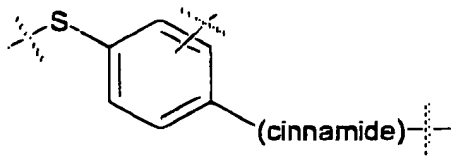
A. Claims 1, 3-23, and 26-60, drawn to compounds, compositions, methods of use, and processes of making compounds, wherein the phenyl group is substituted with a cinnamide group placed *para-* to the linking sulfur atom (*e.g.*, compounds of generic Formulas I and III, where R3 is a cinnamide).

B. Claims 1, 2, 12, 14-15, 17-23, 26, 31-36, and 52-60, drawn to compounds, compositions, methods of use, and processes of making compounds, wherein the phenyl group is substituted with a cinnamide group placed *ortho-* to the linking sulfur atom (*e.g.*, compounds of generic Formula I, where R1 is a cinnamide).

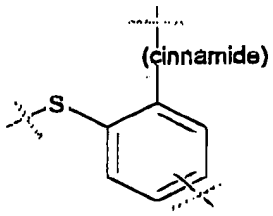
C. Claims 24-25, drawn to compounds, compositions, methods of use, and processes of making compounds of generic Formula II.

Although Applicants do not agree with the propriety of an Election/Restriction requirement at this time, to advance prosecution of this case, alternate Groups A-C are proposed above. Each of the compounds within Groups A-C share a common structural feature. The common structural features for each group are shown below (the waved lines represent points of variable attachment):

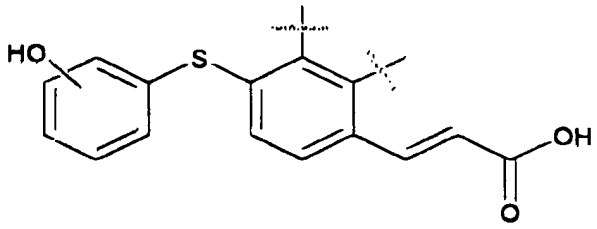
Group A:



Group B:



Group C:



In view of the common structural features and common utility of the compounds of the present invention as discussed above, the Examiner is urged to accept the above-proposed restriction/election. If the above-proposed restriction/election is not at this time acceptable to the Examiner, the Applicants respectfully request further discussion regarding the restriction of the invention under 35 U.S.C. §121.

D. Provisional Election.

If the Examiner accepts the alternative classification, Applicants elect Group A, with traverse, and provisionally elect the species [3-(4-Carboxypiperidin-1-yl)phenyl] [2,3-bis(trifluoromethyl)-4-(E-((4-morpholino)carbonyl)ethenyl) phenyl]sulfide (Compound 4233, Specification, page 383) with traverse.

For the elected species, in Formulas I and III, Ar represents a substituted aryl, substituted with a substituted heterocycle, R_1 and R_2 represent haloalkyl, R_3 represents cinnamide, R_4 represents hydrogen, and R_5 represents hydrogen. In addition for Formula I,

for the elected species, R_3 is "trans-cinnamide," R_8 and R_9 each represent hydrogen, and R_{10} and R_{11} are taken together with N to form a heterocyclyl group.

Claims 1, 4, 6, 8, 9, 10, 11, 12, 16, 18-23, and 26-59 are readable on this species.

If the Examiner does not accept the alternative classification, Applicants provisionally elect Group V as shown on page 9 of the present Office Action, with traverse, for the sake of responding fully to this Office Action.

III. Response to the Examiner's Comments Regarding Claim and Specification Amendments

No formal new matter rejection/objection to the new claims, claim amendments, or specification amendments has been made in the present Action. However, the Office Action dated February 27, 2002 comments, on page 1, that amended claims 1-18 and 20-26, and new claims 27-60 add new matter because "[n]ew Claims 27-60 together with amended Claims 1-18, 20-26 claim subject matter not included in original claims and are therefore broader in scope than the original claims as evident by creation of new Formula III of claims 37-38 independent of claim 1 . . ." The Action also states on page 2 that "claim 1 Formula I and its genus as recited originally, can not accommodate the applicants claimed molecules and structures by the very limited definitions for the specific Aryl, phenyl, heterocyclyl, -NR10R11 . . . ."

Applicants do not dispute that new claims 37 and 52 are broader in scope than original claim 1, at least in some respect, and that generic Claim 1, as amended, is broader in scope than Claim 1 as originally filed. However, Applicants do not agree that the amendments and new claims add new matter. New claims and claim amendments that are broader than the claims as originally filed can be added to an application and this does not constitute new matter provided that there is support for the new claims and claim amendments in the specification as originally filed. MPEP § 2163.07. ("Amendments to an application which are supported in

the original description are NOT new matter." Emphasis in original.) In establishing a disclosure, an applicant may rely not only on the description and drawing(s), but also on the original claims. MPEP § 608.01(l). In the present case, the written description portion of the specification contained subject matter that was not within the scope of the claims as originally filed. The new claims and claim amendments now claim this subject matter. Applicants would like to point out that for each claim amendment and new claim, the basis for the amendment or new claim, in the specification *as originally filed*, was dutifully described in the Response dated December 27, 2001. For example, Claim 1 was amended to add substituents to the definitions of R1-R5, R10 and R11, and Ar. The "Summary of the Invention" portion of the specification was also amended accordingly. Support for each added substituent, taken from the remainder of the specification *as originally filed*, was described on pages 184-186 and 192 of the Response dated December 27, 2001. New Claims 37-51 are directed to substituted diaryl sulfide cinnamide compounds. Diaryl sulfide cinnamide compounds are described on pages 4-10, and pages 63-70 of the Specification *as originally filed*. Support in the specification for these new claims was described more fully on pages 193-194 of the Response dated December 27, 2001. Accordingly, Applicants reiterate that the new claims and claim amendments do not constitute addition of new matter.

The Examiner also comments on page 1 of the Office Action that "the specification as amended constituted new matter wherein terms *e.g.*, Aryl, phenyl, heterocyclyl, -NR10R11 are redefined to increase the scope of the claimed invention." Applicants do not agree that the amendments to the specification add new matter. Amendments to a specification can properly be made and will not constitute the addition of new matter so long as there is basis in the body of the specification and/or claims as originally filed for supporting such amendments. MPEP §§ 2163.06 (III.); 2163.07. In the present case, certain substituents, and compounds having such substituents, were originally disclosed in the claims or in other sections of the application. These amendments to the specification do nothing more than incorporate these already disclosed substituents into the "Detailed

Description" section of the specification. For example, the definitions of alkyl, amino, aryl, etc., in the "Detailed Description" as amended, incorporate substituents that were originally listed in the claims and "Summary of the Invention" as examples for these defined groups, or add substituents that were originally described as Examples, but not listed in this section of the specification. Again, Applicants would like to point out that for each specification amendment, the basis for the amendment in the specification *as originally filed*, and/or claims *as originally filed* was dutifully described in the Response dated December 27, 2001. Accordingly, all of these amendments are proper in form, and do not constitute the addition of new matter.

No formal new matter rejection/objection to the new claims, claim amendments, or specification amendments has been made in the present Action, contrary to the requirements of PTO practice and procedures. If the Examiner has any formal rejections/objections to the amendments submitted in the previous Response and Amendment, Applicants request that the Examiner identify the particular amendment involved and point out the basis for asserting that such amendment is not supported by the specification or claims as originally filed. *See*, MPEP § 608.04. Otherwise, Applicants request entry of the amendments submitted in the Response and Amendment dated December 27, 2001.

IV. Response to the Double Patenting Rejection

A. The Rejection Under 35 USC § 101.

The Office has rejected Claims 1-60 under 35 USC § 101 for statutory type double patenting over issued US Patent No. 6,110,922, as stated in numbered paragraphs 6 and 7 of the present Office Action. Applicants respectfully traverse the statutory type double patenting rejection and request withdrawal of the rejection based on the following remarks.

A 35 USC § 101 statutory double patenting rejection is based on double patenting of the "same invention." Under USPTO guidelines, "the term 'same invention,' in

this context, means an invention drawn to **identical** subject matter." MPEP § 804 (II.), (emphasis added).

The invention claimed in the present Application and the invention claimed in US Patent No. 6,110,922 are not identical. For example, Claim 1 of the present Application has the following substituents that are not present in Claim 1 of US Patent No. 6,110,922:

i) heterocyclylsulfanyl for the R_1, R_2, R_3, R_4, and R_5 definition;

ii) unsubstituted heterocyclyl, heterocyclylamino, substituted heterocyclyl, substituted heterocyclylalkyl, unsubstituted aryl, arylalkyl, carboxyalkyl, and alkoxyalkyl for the definition of R_{10} and R_{11};

iii) carboxyalkyl, aminoalkyl, carboxamido, cyano, unsubstituted tetrazolyl, substituted tetrazolyl, alkanoylaminoalkyl, sulfonate, alkylsulfonylaminocarbonyl, arylsulfonylaminocarbonyl, heterocyclylsulfonylaminocarbonyl, alkenoxycarbonyl, alkoxycarbonylalkylaminocarbonyl, aryl(carboxy)alkylaminocarbonyl, carboxyalkylaminocarbonyl, heterocyclylalkyl, hydroxyalkylaminocarbonyl, hydroxyaminocarbonyl, hydroxy(carboxy)alkylaminocarbonyl, hydroxy(carboxy)alkylcarbonyl, and sulfoalkylaminocarbonyl for the definition of R_{10} and R_{11} taken together with N; and

iv) alkoxyalkyl, aminocarbonyl, unsubstituted heterocyclyl, substituted heterocyclyl, carboxy, carboxyalkyl, carboxyalkoxy, carboxythioalkoxy, carboxycycloalkoxy, alkylsulfanyl, hydroxycarbonylalkyl(carboxyalkyl), hydroxyalkylaminocarbonyl, carboxyalkylamino, carboxyalkenyl,

and alkoxycarbonylalkenyl for the definition of substituents on Ar.

The other independent claims pending in the present Application, Claims 24, 37, 38, 47, 48, and 52, and the claims depending from them, are also not identical to any claim in issued U.S. Patent No. 6,110,922. Accordingly, since the claims of the present application and the claims of US Patent No. 6,110,922 do not claim identical subject matter, a rejection under 35 USC § 101 is not proper. Withdrawal of this rejection is respectfully requested.

B. The Nonstatutory Provisional Double Patenting Rejection.

The Office has provisionally rejected Claims 1-60 for nonstatutory double patenting over co-pending US Application Serial No. 09/695,040 as stated in numbered paragraphs 8-9 of the present Office Action. Applicants note that the nonstatutory double patenting rejection is provisional and that no claims are presently allowable in either the present application or co-pending Application Serial No. 09/695,040. Accordingly, Applicants will address the issue of nonstatutory double patenting if and when any claims are allowed in Application Serial No. 09/695,040.

V. Response to the 35 USC § 112 Rejection.

The Office has rejected Claims 1-60 under 35 USC § 112, first paragraph, as stated in numbered paragraph 10 of the present Office Action. Applicants respectfully traverse the § 112, first paragraph, rejection and request withdrawal of the rejection.

A. The Examiner's Burden of Establishing That The Specification Is Not Enabling Has Not Been Met.

The legal standard for enablement is met if the specification teaches one of ordinary skill in the art how to make and use the invention without undue experimentation. 35 USC § 112, first paragraph. To support a nonenablement rejection, the Examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the

claimed invention. *In re Wright*, 999 F.2d 1557, 1562; 27 USPQ2d 1510, 1513 (Fed. Cir 1993). When an applicant asserts that the specification contains enablement commensurate in scope with the claims, a rejection on the basis of lack of enablement must be withdrawn unless the Examiner substantiates the rejection by reason or evidence. Thus the CCPA, in *In re Budnick*, 190 USPQ 422, observed:

> Where an applicant has asserted that a specification contains enablement commensurate in scope with the protection sought by the claims, but the Examiner is of the opinion that the disclosure is not enabling, he has the burden of substantiating his doubts concerning enablement with reason or evidence.

In the present case, it is noted that the Office has not asserted any specific reasoning or evidence that the specification is not enabled for the process of making the compounds of the claimed invention. However, for the sake of completeness, Applicants submit that the specification discloses how to make 443 compounds within the scope of the invention and that this disclosure satisfies the "how to make" requirement of the enablement test.

Regarding the "how to use" requirement of the enablement test, the Office asserts that "[t]he specification does not give any guidance as to the method for suppressing immune response by way of inhibitory activity in an ICAM/LFA-1 biochemical interaction or ICAM-3/JY-8 cell adhesion [assay] for treating a mammal suffering from a generic inflammation disorder which could be treated using instantly claimed step of administering a composition comprising a compound selected from claim 19 or 47." Contrary to this assertion, the specification clearly gives ample guidance regarding the use of the presently claimed compounds and compositions for suppressing immune response by inhibiting the LFA-1/ICAM biological interaction. Applicants submit that the remaining requirement for enablement (*i.e.*, the "use" of the compounds of the claimed invention without undue experimentation), is satisfied by: (1) the Specification itself; and (2) the scientific articles cited in the Specification and incorporated by reference therein.

First, Applicants note that the specification:

(a) states that the compounds defined by the invention, and compositions containing them, are useful for treating inflammatory and immune diseases (*see, e.g.*, Specification, page 1, lines 9-10; page 4, lines 6-12; and pages 412-416).

(b) contains extensive teaching of the way in which the compounds and compositions can be prepared and used for such treatments, including dosages (*see, e.g.*, Specification, pages 63-70);

(c) discloses a specific assay method for determining if a compound inhibits the ICAM-1/LFA-1 biochemical interaction, and discloses cell based assays, which measure the ability of a compound to block a human cell line that expresses LFA-1 to immobilized ICAM-1 (Specification, pages 404-410);

(d) discloses that the compounds of the invention were tested *in vitro;* and represents that these compounds have biological activity (Specification page 406, lines 1-2; page 407, lines 13-14; and page 409, lines 6-7); and

(d) lists numerous scientific articles disclosing test methods, which illustrate how compounds of the invention can be used to treat specific diseases (Specification, pages 412-416).

It is clear that the disclosure teaches biological assays for determining activity and the specification states that the disclosed representative examples were tested and have biological activity. The disclosure provides sufficient guidance such that one of ordinary skill in the art is taught how to prepare the claimed compounds and assay these compounds for biological activity.

B. The Disclosure is Enabling Because Undue Experimentation Is Not Required.

In support of the § 112, first paragraph rejection, the Office cites the *In re Wands* factors. In addressing the *In re Wands* factors, the Office asserts the following:

(a) The nature of the pharmaceutical art(s) is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities.

(b) There is no absolute predictability even in view of the seemingly high level of skill in the art.

(c) The existence of these obstacles would prevent one of ordinary skill in the art from accepting any medicinal or therapeutic regimen on its face.

(d) The instant specification does not give any guidance as to the full range of treatment involving use of derivatives of diarylsulfide by using the instantly claimed step of administering a compound or composition of claims 19 or 41.

(d) In order to practice the claimed invention, one skilled in the art would have to speculate which disease could be treated by using the claimed derivatives found in the instant claim 4.

(e) The number of possible diseases &/or conditions embraced by the claims would impose undue experimentation on the skilled art worker.

Office Action, pages 15-16.

Based on this analysis of the In re Wands factors, the Office concludes that "the broad terminology is not enabled because the metes and bounds of the diseases which could be treated by using the derivatives found in the instant claims and the same can not be ascertained." Office Action, page 16.

In response, Applicants respectfully submit that the specification teaches one of skill in the art how to make and use the full scope of the claimed invention without "undue experimentation" and request consideration of the following comments.

First, in evaluating a claim for lack of enablement, MPEP § 2164.01(c) directs that "[i]f a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." In the present case, as noted above, the specification states that the compounds defined by the invention, and compositions containing them, are useful for treating inflammatory and immune diseases (*see, e.g.*, Specification, page 1, lines 9-10; page 4, lines 6-12; and pages 412-416), thus satisfying the requirements of 35 USC § 112.

Next, MPEP § 2164.01(c) directs that "[w]hen a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation." In the present case, Claims 20-23, and 48-51 are the only claims limited by a particular use. The use specified in these claims is either a method of inhibiting inflammation, a method of suppressing immune response, or a method for the treatment of an inflammatory condition. As noted above, the specification contains extensive teaching of the way in which the compounds and compositions can be prepared and used for such treatments, including dosages (*see, e.g.*, Specification, pages 63-70).

In contrast, MPEP § 2164.01(c) directs that "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use." As noted above, the specification lists numerous scientific articles disclosing test methods which demonstrate how compounds of the invention can be used to treat specific diseases (Specification, pages 412-416). Based on this assertion in the specification, the enablement rejection must include an explanation why the specification fails to enable each disclosed use. Under USPTO practice and procedure, if any of these uses are enabled, the application is enabled for the claimed invention.

Regarding the assertion of the Office that "[t]he nature of the pharmaceutical art(s) is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities," as noted above, the compounds of the invention have been tested *in vitro*. Although the testing is *in vitro*, *in vivo* testing is not required for enablement, provided there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity. See, MPEP § 2164.02. Here, the specification discloses compounds that are identified by a biological assay to block the interaction between the integrin LFA-1 and its adhesion partners, the ICAMs. The specification asserts that a compound that blocks

the ICAM/LFA-1 interaction suppresses an inflammatory response (Specification, page 4, lines 2-4.), and that the effect of ICAM/LFA-1 inhibitors has been demonstrated in animal models (Specification, pages 412-416). Applicants believe that this disclosure is clearly sufficient to establish reasonable correlation between the demonstrated the *in vitro* testing and the claimed *in vivo* utility. If, however, the Office concludes despite this evidence that there is a lack of correlation between the *in vitro* and *in vivo* testing, Applicants request that the Office give reasons for this conclusion as required in MPEP § 2164.02 so that Applicants can appropriately respond to such a rejection.

Finally, Applicants respectfully do not agree with the assertion of the Office regarding the remainder of the *In re Wands factors*, as stated in paragraphs (b)-(e) above, and the conclusion that "[t]he broad terminology is not enabled . . ." It is Applicants' position that these assertions do not establish that undue experimentation is required to make and use the invention. "Absolute predictability" and acceptance of "any medicinal or therapeutic regimen of its face" are not required for enablement. What is required is that one skilled in the art "can extrapolate the disclosed or known results to the claimed invention" and "anticipate the effect of a change within the subject matter to which the claimed invention pertains . . ." *See*, MPEP § 2164.03. Further, "it is well settled, that patent applications are not required to disclose every species encompassed by the claims, even in unpredictable art." *In re Vaeck*, 947 F.3d 488, 496 (Fed. Cir. 1991); *See, also, In re Anderson,* 176 USPQ 331 (1973). The mere fact that a claim is broad in scope does not provide a reasonable basis for a rejection for lack of enablement. Disclosure of species using broad terminology and illustrative examples is an accepted method of satisfying the enablement requirement and can fully support the scope of the claims. *See, In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *In re Angstadt*, 537 F.2d 498 (CCPA 1976). In the present case, the specification teaches 443 representative examples with biological activity and teaches biological assays for determining activity of additional specifically unnamed compounds within the scope of the invention. It would be onerous and redundant to require Applicants to prepare each and every conceivable

additional species encompassed within the scope of the invention and test these for each disclosed disease to satisfy the enablement requirement and the law does not require the same.

As demonstrated above, it is evident that the specification provides ample guidance for selecting embodiments of the invention and testing these embodiments for the desired utility. The extensive teachings in the specification and articles referenced therein support Applicants' position that those skilled in the art will not have to carry out undue experimentation to identify unnamed active compounds within the scope of the claimed invention and identify a disease which could be treated by the active compound. Accordingly, Applicants submit that the content of the disclosure, including the references cited therein, precludes a finding of undue experimentation and request withdrawal of the rejection under 35 USC § 112, first paragraph.

VI. Response to the 35 USC § 103 Rejection.

The Office has rejected Claims 1-60 under 35 USC § 103, as unpatentable over the cited Franke et al reference. Applicants respectfully traverse the § 103 rejection and request reconsideration and withdrawal of this rejection.

The basis for the § 103 rejection by the Office is stated in numbered paragraph 11 of the present Office Action. Applicants respectfully traverse this basis for rejection. It is Applicants' position that (1) the Office has not provided the necessary suggestion or motivation to modify Franke et al. to arrive at the compounds of Applicants' invention; and (2) the skilled artisan would have no reasonable expectation of success in modifying Franke et al. to arrive at Applicants' invention. Therefore, a *prima facie* case of obviousness has not been established. Accordingly, Applicants request withdrawal of this rejection.

A. The Requisite Motivation Supporting the Modification of The Prior Art Has Not Been Provided.

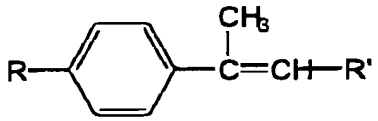
To establish a *prima facie* case of obviousness, the Office must provide a suggestion or motivation, either in the references themselves or in the knowledge generally

available to one of ordinary skill in the art, to modify the reference, or to combine reference teachings. MPEP § 2143. It is Applicants' position that the Office has not provided this suggestion or motivation and thus has not established a *prima facie* case of obviousness.

1. The Differences Between the Prior Art Compounds and Applicants' Invention Do Not Support Prima Facie Obviousness Based on "Structurally Similar Compounds"

It is evident that the compounds disclosed in the Franke et al. reference differ structurally from those of Applicants' claimed invention. At the very least, Franke et al. does not disclose substitution on an aryl ring of a diaryl sulfide cinnamide compound. Franke et al.'s unsubstituted compounds are not within the scope of Applicants' claimed invention. (See, *e.g.*, Claim 1, proviso (ii)). To support a *prima facie* case of obviousness, the Office must demonstrate that the prior art provides motivation to make the substitutions necessary to arrive at Applicants' invention.

Franke et al. discloses a generic class of compounds, shown below, and labeled as Formula A.



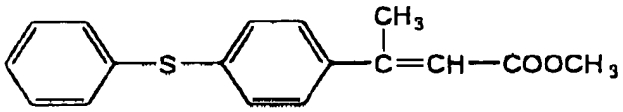
Formula A

Franke et al., Table 1, pages 273-275.

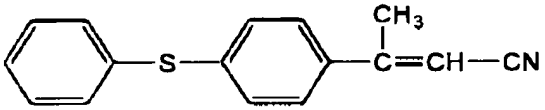
Formula A shows a 1,4 substituted phenyl group, substituted with a variable R group, and an allyl group substituted with a variable R' group. No substitution, other than the variable R group, and the allyl group, substituted with a variable R' group is shown on the phenyl group.

The Franke et al. reference discloses 93 compounds within the generic compound class shown above (*i.e.*, Compound Nos. 22-114). Various substituents for the R

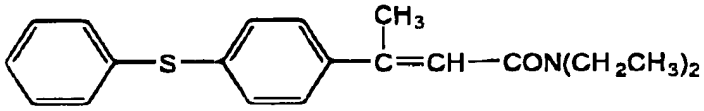
group are disclosed in Franke et al. including phenyl, alkyl, aryloxy, and alkoxy groups, among others. Of the 93 compounds disclosed in Franke et al., only three compounds (i.e., Compound Nos. 47-49, shown below) have an R group that is an aryl sulfide.



Compound 47



Compound 48



Compound 49

Franke et al., Table 1, Compound Nos. 47-49.

As the Examiner can see from the above compounds, substituted diaryl sulfides are not described by Franke et al. All of Franke et al.'s bi-phenyl thioethers are completely unsubstituted on both aryl rings. None of these compounds disclose the limitation in all of Applicants' claims that these diarylsulfide cinnamides be "substituted."

For the R' group, Franke et al. discloses various substituents including nitrile, carboxy, carboxy alkyl, and amide (See, e.g., Table 1, Compounds 22-114). Only one of Franke et al.'s diaryl sulfides, Compound 49, is a "cinnamide," which is another limitation of all of Applicants' claims.

The Office has not supplied a reference showing the required motivation to make the necessary changes to modify Franke et al.'s sole diaryl sulfide "cinnamide" compound to arrive at Applicants' claimed invention. Instead, the Office seeks to establish a *prima facie* case of obviousness based on the statements that "it would have been obvious to

one having ordinary skill in the art at the time of invention to prepare instant compounds by modifying the core of generic Formula of reference Franke et al . . . and prepare derivatives by putting/inserting extra rings [sic] structures including heterocycles . . . and make the compounds as claimed herein, and also tryout the use/utility different or similar to reference Franke et al. . . ." The Office asserts that "[t]he motivation stems from the expectation of making compounds having equal or better pharmacological activity but also compositions for treating inflammation and conditions/diseases as recited herein," and seeks to establish a *prima facie* case of obviousness based on the concept of "structurally similar compounds." Office Action, page 18.

However, the mere possibility that one skilled in the art might find it obvious to try the claimed invention is not a legitimate test of patentability. To establish a *prima facie* case of obviousness, the Office must show something more than that the invention was obvious to try. The Office must show that the prior art motivated the skilled artisan to make the claimed invention. Moreover, the requisite teaching or suggestion to modify a reference must be found in the prior art, and cannot be derived from Applicants' own disclosure. *See*, MPEP § 2143; MPEP § 2141.

> To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988).

More specifically, in the case of chemical inventions, "[f]or a chemical compound, a *prima facie* case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . **where the prior art gives reason or motivation to make the claimed composition**.'" *Yamanouchi Pharmaceutical Co., Ltd., and Merck & Co., Inc., v. Danbury Pharmacal, Inc.*, 231 F.3d 1339; 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000) (emphasis

added). Here, the Office has not identified any such reason or motivation and has not met its burden of establishing a *prima facie* case.

In assessing the patentability of a claimed compound over a prior art compound, the issue is whether the prior art suggests substituting one moiety for another with an expectation of obtaining similar properties. *See, Ex parte Brouard*, 201 U.S.P.Q. 538 (Bd. Pat. App. 1976) (The lack of suggestion in the prior art to substitute a hydrogen atom for a hydroxy group in a compound used for dyestuffs led to the reversal of an obviousness rejection); *In re Grabiak*, 769 F.2d at 732, 226 U.S.P.Q. at 872 (Fed. Cir. 1985) (Patent and Trademark Office failed to establish a *prima facie* case of obviousness of invention relating to class of chemical compounds having utility as herbicidal safeners where there was inadequate support in the prior art for ester/thioester change in structure of prior art herbicidal safener).

Here, Franke et al. does not suggest making any of the changes needed to arrive at Applicants' invention, and the Office has not adduced any other specific teaching that would motivate making such changes to the Franke compounds. Thus, because the Office has not provided a reference that suggests modifying the Franke et al. reference to arrive at Applicants' claimed invention, no *prima facie* case of obviousness has been established.

2. Franke et al. Does Not Disclose Compounds Used to Treat Inflammatory Diseases.

The Office states that "Franke et al teaches making [sic] of substitued biaryl/phenyl thioethers as evident from Table 1, compound No. 47 . . ." and that Franke et al. also "teaches the use of compounds having Juvenilhormone activity." (Office Action page 17). Applicants do not disagree with this statement. However, the Office has not asserted that Franke et al. teaches the use of compounds for Applicants' asserted utility (i.e., treatment of inflammatory responses), nor has the Office supplied another reference that suggests this utility. Establishing a *prima facie* case of obviousness for chemical compounds requires both structural similarity and utility. *See,* MPEP 2144.09. Merely citing a reference disclosing compounds that are "structurally similar" without additional evidence of the utility of such

compounds is not sufficient to satisfy the Office's burden to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the 35 USC 103(a) rejection.

B. The Prior Art Must Provide a Reasonable Expectation That the Proposed Modification Will Succeed.

The prior art can be modified or combined to reject claims as *prima facie* obvious only so long as the combination establishes a reasonable expectation of success. MPEP § 2143.02.

None of Franke et al.'s three disclosed diaryl thioether compounds have Applicants' claimed aryl substitutions. To arrive at Applicants' invention, without an additional reference suggesting a particular modification, one of skill in the art would have had to: 1) select, from among 93 disclosed compounds, three specific diaryl thioether compounds (*i.e.*, Compounds 47-49); 2) from these three diaryl thioether compounds, select the one "cinnamide" compound (*i.e.*, Compound 49), and 3) manipulate the sole diaryl thioether compound to arrive at Applicants' claimed invention - a substituted diaryl sulfide "cinnamide." However, the Franke et al. reference provides no basis for taking any of these specific steps. Furthermore, Franke et al. does not indicate that the disclosed diaryl thioether compounds have any activity (utility) comparable to the activity of the claimed compounds. Absent any teaching of the desired utility, the skilled artisan would have no reasonable expectation that selecting the diaryl thioether compounds and subsequently modifying such compounds, which are described as having a different utility altogether, would succeed in producing compounds used to treat inflammatory diseases. Accordingly, Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness and request withdrawal of the § 103 rejection.

VII. Correction of the filing date for the Response and Amendment dated December 27, 2001.

The Office Action dated February 27, 2002 indicates that it is responsive to a communication filed on December 29, 2001. Applicants believe that the December 29, 2001 date is a clerical error. The prior communication filed with the US Patent and Trademark Office was a Response and Amendment, filed on December 27, 2001. This communication was addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231 filed with a certificate of mailing, signed and dated on December 27, 2001; and deposited with the US Postal Service with sufficient first class US postage. Accordingly, under 37 CFR § 1.8, Applicants submit that the Response and Amendment dated December 27, 2001 was filed with the US Patent and Trademark Office on December 27, 2001. Having regard for the importance of this date for a timely filing of the Response and Amendment, Applicants request an explicit correction of this date for the record.

VIII. Correspondence Address.

It is noted that the Office Action dated February 27, 2002 was sent to Abbott Laboratories. The undersigned attorney requests that the Examiner address all communications to Jeffrey G. Sheldon, Esq., of Sheldon & Mak, 225 South Lake Avenue, 9th Floor, Pasadena, California 91101 as directed in the Associate Power of Attorney Forms mailed September 13, 2001 and March 28, 2002. A copy of each of these Associate Power of Attorney Forms is being re-sent with this Response. Applicants request that these Associate Power of Attorney Forms be placed in the Examiner's file, if this has not been done already, and Applicants request a change of the Correspondence Address as directed therein.

CONCLUSION

It is believed that this Response is fully responsive to the Office Action dated February 27, 2002. If, however, there are any issues that can be resolved by telephone with the Applicants' representative, the Examiner is encouraged to contact the undersigned directly.

The Commissioner is authorized to charge $430, the amount to cover the cost of the two month extension, to Deposit Account No. 19-2090. The Commissioner is also

authorized to charge any other additional fees, or credit any overpayment, associated with this communication to Deposit Account No. 19-2090.

Respectfully submitted,

SHELDON & MAK
a Professional Corporation

Date: July 29, 2002

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